REMARKS

This responds to the Final Office Action mailed on August 6, 2009.

Claims 1, 21, 23-24, 43, and 62 are amended, claims 5-7, 25 and 65 are canceled, and claims 66-67 are added; as a result, claims 1-2, 9-24, 27, 29-32, 43-44, 48-51, 53, 55-59, 62, and 66-67 are now pending in this application.

Applicant thanks Examiner Kevin Hill for the courtesy of a telephone interview on November 12, 2009 with Applicant's representative Janet E. Embretson and Dr. John Engelhardt.

The 35 U.S.C. § 112 Rejection

Claims 1-2, 5-7, 9-24, 43-44, 46, 48-50, 62, and 65 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for an *in vitro* method to enhance recombinant adeno-associated (rAAV) transduction of a mammalian cell comprising contacting the mammalian cell with at least one rAAV and two different agents that each enhance intracellular rAAV transduction of a mammalian cell in an amount effective to more than additively enhance rAAV transduction, wherein the first agent is doxorubicin and the second agent is the tripeptide aldehyde N-acetyl-L-leucyl-L-leucyl-norleucinal (LLnL) or N-carbobenzoxyl- L-leucinyl-L-leucinyl-L-leucinal (Z-LLL) that inhibits proteosome proteolytic activity, allegedly does not reasonably provide enablement for an *in vitro*, *ex vivo* or *in vivo* method to enhance rAAV transduction of an enormous genus of mammalian cells, nor contacting the mammalian cell with a combination of an enormous genus of at least two or more agents in an amount effective to more than additively enhance rAAV transduction. This rejection is respectfully traversed.

It is Applicant's position that is it within the skill of the art to determine a serotype of AAV and proteasome modulator useful to transduce a particular type of mammalian cells. Evidence to support that position is provided in, for example, Hacker et al. (J. Gene Med., 7:1429 (2005)) (copy enclosed), which disclose the relative efficiency of infecting 6 different cancer cell lines (including cervical, breast, prostate and colon carcinoma cell lines) and 3 patient samples with 5 different AAV serotypes (see Figures 1-4). It is also disclosed that a proteasome modulator enhanced transduction of cells with 4/5 of those serotypes (see Figure 6). Denby et al.

(Gene Ther., 12:1534 (2005)) (copy enclosed) disclose infecting human primary endothelial cells and murine vascular endothelial cells with 3 different AAV serotypes in the presence or absence of 2 different proteasome modulators. Tang et al. (BBRC, 331:1392 (2005)) (copy enclosed) relate that combined treatment with proteasome modulating agents enhanced AAV-2 transduction in a variety of different intestinal epithelial cell lines. Further, transduction of keratinocytes by AAV-2 was reported to be enhanced by a proteasome modulator (see Braun-Falco et al., Arch. Dermatol. Res., 296:528 (2005); copy enclosed). Moreover, enhanced transduction of cells with AAV was observed when a proteasome modulator was added 13 days after infection (see Jennings et al., Mol. Thera., 11:600 (2005); copy enclosed, and Yan et al., J. Virol., 78:2863 (2004) (of record)).

It is also Applicant's position that is it within the skill of the art to administer AAV and a proteasome modulator to an animal *in vivo*. For instance, Monahan et al. (Thromb. Haemostasis, 7:OC-TH-097 (2009); copy enclosed) disclose that in a mouse and dog model of human hemophilia, the administration of a proteasome modulator (intravenously in the dog model) and rAAV encoding factor VIII (via the portal vein in the dog model) enhanced factor VIII expression. Nathwani et al. (Gene Ther., 16:60 (2008)) (copy enclosed) disclose that tail vein administration of a proteasome modulator to mice 24 hours before rAAV administration (via the tail vein) enhanced transgene expression. In addition, U.S. Patent No. 7,122,335 discloses administering AAV and a proteasome modulator intranasally as well as via the portal vein. Further, the abstract for Finn et al. (Mol. Thera., epub Nov 10, 2009) (copy enclosed) discloses that the FDA approved proteasome inhibitor bortezomib enhanced AAV-2-mediated gene expression *in vivo*.

In support of the position that the preparation of a wide variety of rAAVs is within the skill of the art and that a large number of different rAAVs have been prepared, Applicant previously submitted documents including the abstracts for Sarkar et al., Blood, 103:1253 (2004); Arruda et al., Blood, 103:85 (2004); and Harding et al., Hum. Gene Thera., 17:807 (2006)). In support of the position that AAV is known to have a broad host range, Applicant previously submitted documents including Denby et al., Gene Ther., 12:1534 (2005) and Douar et al., J. Virol., 75:1824 (2001). For the Examiner's convenience, a copy of each of those documents is enclosed herewith.

Moreover, it is Applicant's position that it is within the skill of the art worker in the relevant art to determine the amount of agents and routes of administration. In re Johnson, 282 F.2d 370, 127 U.S.P.Q. 216 (C.C.P.A. 1960) (the selection of suitable dosages is within the skill of the art). See, e.g., Monahan et al., *supra*; Nathwani et al., *supra*; U.S. Patent No. 7,122,335; and Finn et al., *supra*.

Likewise, with regard to any purported toxicity, it is Applicant's position that it is within the skill of the art worker in the relevant art to select a nontoxic amount of an agent for administration. See, e.g., Nathwani et al., *supra*, and U.S. Patent No. 7,122,335. In this regard, the Examiner is requested to consider the Supplemental Rule 132 Declaration, executed by two of the named co-inventors of the present application, enclosed herewith. In that Supplemental Rule 132 Declaration, Drs. Engelhardt and Yan disclose data from preliminary toxicity studies with agents falling within the scope of the claims, e.g., Doxil® and Z-LLL.

Therefore, one of skill in the art can select an AAV serotype useful to transduce a particular cell type and a route to administer that AAV and a compound. In addition, in view of Applicant's disclosure, it is within the skill of the art worker to select a specific combination of compounds to enhance transduction of a particular AAV and to select routes to administer that combination and AAV.

Accordingly, withdrawal of the 35 U.S.C. § 112, first paragraph, rejection is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(612) 373-6959

Date December 7, 2009

By 
Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 C.F.R 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 7 day of December, 2009.

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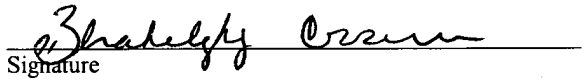
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